REMARKS

Introductory Comments

As of the mailing date of the 03/29/2010 Office Action, claims 16-31 were pending in the present application. In the present Response, no claims have been canceled, amended, or added, so claims 16-31 remain for consideration upon entry of the present Response. Reconsideration and allowance of the claims is respectfully requested in view of the following remarks.

Provisional Nonstatutory Double Patenting Rejections

Claims 16 and 22 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14 and 20 of the copending application published as Application Publication No. 2007/0105746 A1. 03/29/2010 Office Action, paragraph spanning pages 2 and 3.

Applicants thank the Examiner for pointing out the potential obviousness-type double patenting issue between the claims of the present application and those of the copending application published as Application Publication No. 2007/0105746 A1. In view of the possibility that claims in the cited application or the present application will be further amended before allowance, Applicants will defer responding to this provisional rejection until claims in the reference application are allowed, claims in the present application are otherwise allowable, and it is determined whether this provisional rejection becomes an actual rejection.

Applicants also respectfully note that the present application was filed before the cited application. Accordingly, the present provisional rejection should be withdrawn if it becomes the sole remaining rejection. See MPEP 804(I)(B)(1) ("If a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.").

Anticipation Rejections over Domb

Claims 16-20, 22 and 25-29 stand rejected under 35 U.S.C. § 102(b) as anticipated by Domb (US Patent 5188837, Published 02/23/1993). 03/29/2010 Office Action, page 4, third full paragraph. Applicants respectfully traverse this rejection.

U.S. Patent No. 5,188,837 to Domb (hereinafter "Domb") generally describes a microsuspension system and method for its preparation. Domb abstract. The microsuspension contains lipospheres, which are solid, water-insoluble microparticles that have a layer of a phospholipid embedded on their surface. Domb abstract. The core of the liposphere is a solid substance to be delivered, or a substance to be delivered that is dispersed in an inert solid vehicle, such as a wax. Domb abstract. In Domb Examples 1 and 10, cited by the Office, the weight ratio of lipid phase to aqueous phase is approximately 1:12.5. Domb, column 6, lines 25-40; column 8, lines 44-53.

Before addressing the present anticipation rejection, a few comments on the present invention are in order. All currently pending claims include or further limit the limitations of independent claim 16. In step a) of Applicants' claim 16 method, the active compound is mixed with the wax-based, polymer-based, or lipid-based active compound vehicle and an emulsifier to form a phase B. The mixing is carried out at a temperature above the melting or softening point of the active compound vehicle. In step b), the phase B from step a) is mechanically mixed with an aqueous phase A at a **specified weight ratio without high-pressure homogenization,** again at a temperature above the melting/softening point of the used active compound vehicle, to form a **lyotropic liquid-crystalline mixed phase.** As stated in the present application,

> It has been found in accordance with the invention that aqueous active compound vehicle dispersions . . . can be produced advantageously if a lipid melt is mixed with an aqueous phase that has been heated to same temperature in a **defined weight ratio of 1:5 to 5:1**.

Present application, page 5, second paragraph (emphasis added). Further, the present application states, "By observing the proportions of phases A and B it is possible to achieve a very strong mixing action even with the input of low shearing energies."

Present application, sentence bridging pages 5 and 6. Accordingly, the use of the specified weight ratio of phases A and B and the other features of claim 1 enable the production of aqueous vehicle dispersions with vehicle particles having diameters in the nano-range without high-pressure homogenization. Thus, the present invention provides a significant advantage for producing nanoparticles by dispensing with the requirement for high-pressure homogenization. The cited references Domb and Speiser do not teach the Applicants' claim 16 phase B to phase A weight ratio of 1:5 to 5:1.

Moreover, the nanoparticles and dispersions obtained according to the invention are different from those of the cited references. In the reference nanoparticles, a solid core of the active compound vehicle is surrounded by an emulsifier layer. In contrast, the nanoparticles according to the invention comprise **emulsifiers in the interior of the nanoparticles** and are built up from one or more membranes, i.e., they have membrane-structures. See, e.g., the present application at the paragraph bridging application pages 6 and 7, and claim 26. The membrane structure of the nanoparticle spans the entire nanoparticle. So, there is a substantially larger membrane surface area into which large amounts of pharmaceutical, cosmetic and/or food technology compounds can be embedded. Since the active compounds are stored not only in the surface region of the nanoparticles, but also throughout the nanoparticles, the invention enables the highly targeted release of the active compounds, also over a prolonged period of time.

The lyotropic liquid-crystalline mixed phase obtained in step b) of the claimed method displays the behavior of a **single phase**. See, e.g., present application page 6, lines 4-9. This is in contrast to the production of the reference emulsions where the product emulsion displays the behavior of two phases.

When the lyotropic liquid-crystalline mixed phase of step b) of the claimed method is diluted with an aqueous phase, as recited in step c), the mixed phase is divided and dispersed in the aqueous phase in the form of small particles yielding a dispersion.

Having briefly reviewed the present invention, Applicants respectfully assert that claims 16-20, 22, and 25-29 are not anticipated by Domb for at least two reasons. First,

Domb does not teach Applicants' claim 16 phase B to phase A weight ratio of 1:5 to 5:1. Second, the particles produced by the claim 16 method and those produced by the method of Domb have a different physical structure.

"Because the hallmark of anticipation is prior invention, the prior art reference – in order to anticipate under 35 U.S.C. § 102 – must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements "arranged as in the claim."" *Net MoneyIn v. Verisign*, No. 2007-1565, slip op. at 15, 2008 WL 4614511 at *8, (Fed. Cir. 2008) (*quoting Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)).

First, Domb does not anticipate Applicants' claims because Domb does not teach Applicants' claim 16 phase B to phase A weight ratio of 1:5 to 5:1. Claim 16, clause b) requires a weight ratio of phase B to phase A of 1:5 to 5:1. All of Applicants' other pending claims include or further limit all the limitations of claim 16. Domb does not teach Applicants' claim 16 phase B to phase A weight ratio of 1:5 to 5:1. The Office Action cites two working examples of Domb. In Domb Example 1, the weight ratio of B:A is about 1:12.5 (using the sum of 0.100 gram lidocaine, 0.500 gram tristearin, and 0.200 gram L-α-lecithin as phase B, and 10 milliliters (approximately 10 grams) of aqueous buffer as phase A). Domb, column 6, lines 25-40. And in Domb Example 10, the weight ratio of B:A is again about 1:12.5, with the only difference being that 0.500 gram polycaprolactone is substituted for the 0.500 gram tristearin in Example 1. Domb, column 8, lines 44-53. Although not cited by the Office, Examples 1, 3, 5, 6, and 9 of Domb appear to have the same B:A weight ratio of 1:12.5. The highest phase B to phase A weight ratio in Domb appears to be the 1:10 ratio of Examples 8 and 17. So, Domb does not teach Applicants' claim 16 B:A weight ratio of 1:5 to 5:1. For this reason alone, Domb does not anticipate any of Applicants' claims.

Moreover, Domb uses the conventional approach with homogenization under high shear forces, "using homogenizers, and sonication techniques". Domb, column 6, lines 4 to 6. And in Examples 1 and 10 (and further Examples) of Domb, "the formulation was

mixed well by vigorous hand shaking and by vortex for about 5 minutes". Domb, column 6, lines 35-36, and column 7, lines 19 and 36-37.

Second, Domb does not anticipate Applicants' claims because the particles produced by the claim 16 method and those produced by the method of Domb have different physical structures. In Domb, the lipospheres have a core of a solid substance to be delivered or a substance to be delivered that is dispersed in an inert solid vehicle, and a layer of phospholipid coating surrounding the core. See, e.g., Domb abstract; column 2, lines 48-54; and column 2, line 66 through column 3, line 6. In contrast, as set forth above, the nanoparticles according to the invention are built up from one or more membranes, i.e., they have membrane structures, and comprise emulsifiers in the interior and on the surface of the nanoparticles. See also the subject matter of claims 26 and 27. Thus, the dispersion according to claim 22, the additive according to claim 25, and the nanoparticles according to claims 26 to 29 are also not anticipated by Domb.

For all of the above reasons, Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 16-20, 22, and 25-29 under 35 U.S.C. § 102(b) over Domb.

Obviousness Rejections over Speiser

Claims 16, 17, 20-22, and 26-29 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Speiser (US Patent 4880634). 03/29/2010 Office Action, page 5, third full paragraph (paragraph no. 1). Applicants respectfully traverse this rejection.

U.S. Patent No. 4,880,634 to Speiser (hereinafter "Speiser") generally describes an excipient system containing a drug for peroral administration in the form of an ultrafine aqueous, colloidal suspension of lipid nano-pellets comprised of lipids and a surfactant of which the particle diameters of the nano-pellets range from 50-1,000 nm, preferably from 80-800 nm, the ratio of lipid to surfactant in the lipid nano-pellets ranging from 1:0.1 to 1:2.2, preferably from 1:0.22 to 1:1.2, especially from 1:1 to 1:0.22, and where the lipid nano-pellets are present in the suspension in a concentration of from

1-20% by weight. Speiser abstract. The lipid nano-pellets can be provided with pharmacologically active substances. Speiser abstract.

Applicants respectfully assert that claims 16, 17, 20-22, and 26-29 are patentable over Speiser because Speiser does not teach or suggest Applicants' claim 16 phase B to phase A weight ratio of 1:5 to 5:1. Claims 26-29 are further patentable over Speiser because Speiser does not teach or suggest the claim 26 requirement for "membranes which infiltrate the entire nanoparticles so that there are emulsifiers in the interior and on the surface of the Nanoparticles".

For an obviousness rejection to be proper, the Examiner must meet the burden of establishing a *prima facie* case of obviousness. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Establishing a *prima facie* case of obviousness requires that all limitations of the claim be taught or suggested by the prior art. *See, e.g., CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003); *In re Royka,* 490 F.2d 981, 985 (C.C.P.A. 1974).

Speiser relates generally to excipient systems for perorally administered drugs. As correctly noted in the penultimate paragraph of page 6 of the Office Action, Speiser teaches in Example 9 a weight ratio of phase B to phase A of 1:8, which is outside the claim 16 range of 1:5 to 5:1. Speiser, column 11, lines 5-21. And, contrary to the Office's assertion, it would not have been obvious for a skilled person to have used Applicants' phase B to phase A weight ratio, i.e. a higher amount of phase B and/or lower amount of phase A than taught in Speiser. In the Examples of Speiser **large amounts of water** are used. See ,e.g., Speiser Example 1 with a 4.8 gram lipid phase (phase B) and a 55.2 gram aqueous (phase A), corresponding to a B:A ratio of 1: 11.5, which well outside the claim 16 B:A weight ratio of 1:5 to 5:1. Speiser's highest ratio of phase B to phase A is 1:7.15 in Example 12, which is again well outside the claim 16 B:A weight ratio of 1:5 to 5:1. There is therefore no teaching or suggestion in Speiser to use Applicants' claim 16 B:A weight ratio of 1:5 to 5:1.

The Office Action states that the amount of water to be added to the lipid phase could be adjusted "to adjust the concentration of the nano-pellets in the dispersion and

therefore the amount of active agent administered". 03/29/2010 Office Action, page 7, first paragraph. It is submitted that is not evident from Speiser that the amount of active agent to be administered is controlled via the amount of water added to the lipid phase during the preparation process of the nano-pellets. The suggested modification of Speiser therefore appears to be based on impermissible hindsight. In particular, it is not evident from Speiser that a skilled person would use lower amounts of water (higher amounts of lipids) than used in the examples of Speiser in order to set the amount of active agent administered. Instead, Speiser discloses a different approach to adjust the amount of active agent administered:

> However, it is also possible to separate the nanopellets from the suspension using methods known per se, or to enrich them. By way of illustration, following ultracentrifuging and ensuing lyophilization, one obtains a powder representing a further stable form. The dry lyophilisate as such can be divided into therapeutic doses (e.g. in the form of a powder, tablets, capsules) and be administered as such.

Speiser, column 8, lines 57-64. Further, it is noted that Speiser makes the dispersions using conventional methods, and conventional methods commonly use clearly higher amounts of water. And a skilled person would expect that it is not possible to significantly decrease the amount of water without adversely affecting the emulsification process used to produce the suspension. Thus, the skilled person would not have tried to adjust the active agent amount by significantly decreasing the amount of water in the emulsification state.

Moreover, Speiser uses the conventional approach for the production of nanoparticles by homogenization. Speiser requires "dispersing . . . under dispersing conditions sufficient to produce lipid nano-pellets of a particle size of from about 50 to 1,000 nm", wherein "As a rule the dispersal step (e.g. the treatment with a high angular speed agitator followed by ultrasonic treatment at suitable frequencies and time intervals) is carried out until the desired lipid particle size of about 50 to 1,000 nm is attained". Speiser, column 3, lines 22-26; column 8, lines 39-43. Therefore, in Speiser the desired particle size is obtained by the dispersing, in contrast to the invention where "a very strong mixing action even with the input of low shearing energies" is achieved by using the specified ratio of phase A to phase B.

Claims 26-29 are further patentable over Speiser. Specifically, claim 26 requires "membranes which infiltrate the entire nanoparticles so that there are emulsifiers in the interior and on the surface of the Nanoparticles". Speiser does not teach or suggest this limitation.

For all of the above reasons, Speiser does not support a *prima facie* case of obviousness against Applicants' claims. Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 16, 17, 20-22, and 26-29 under 35 U.S.C. § 103(a) over Speiser.

Obviousness Rejections over Speiser + De Vringer

Claims 23-25, 30, and 31 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Speiser in view of De Vringer (US Patent 5667800). 03/29/2010 Office Action, page 7, paragraph no. 2. Applicants respectfully traverse this rejection.

Speiser is described above.

U.S. Patent No. 5,667,800 to De Vringer (hereinafter "De Vringer") generally describes an aqueous suspension of solid lipoid nanoparticles, comprising at least one lipid and preferably also at least one emulsifier, for topical application to the body. De Vringer abstract.

Applicants respectfully assert that claims 23-25, 30, and 31 are patentable over Speiser in view of De Vringer for the reasons described above in the context of the obviousness rejection of claim 16 over Speiser alone.

Currently rejected claims 23-25, 30, and 31 each include or further limit all of the limitations of claim 16. As described above, claim 16 is patentable over Speiser because Speiser does not teach or suggest the claim 16 phase B to phase A weight ratio of 1:5 to 5:1. Claims 23-25, 30, and 31 are therefore patentable over Speiser. The addition of De Vringer does not cure the deficiencies of Speiser. Specifically, De Vringer is cited as teaching that "the aqueous dispersion is further mixed with a polyol phase or oil phase".

03/29/2010 Office Action, page 7, last full paragraph. Accordingly, the Office has not established a *prima facie* case of obviousness based on Speiser and De Vringer.

Applicants therefore respectfully request the reconsideration and withdrawal of the rejection of claims 23-25, 30, and 31 under 35 U.S.C. § 103(a) over Speiser in view of De Vringer.

It is believed that the foregoing remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly, reconsideration and allowance is respectfully requested.

It is believed that all the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement with or concession of that rejection, issue or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130 maintained by Applicants' Attorneys.

Respectfully submitted,

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